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ORIGINAL RESEARCH

Circadian Oscillations of Minimal Erythema Dose (MED) are Also Influenced by Diet in Patients with Psoriasis: A Chronomedical Study

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ABSTRACT

Introduction: Minimal erythema dose (MED) remains a parameter of paramount importance to orient narrow-band (NB)-UVB phototherapy in psoriatic (PsO) patients. Recently, circadian rhythm and diet were recognized as potential MED modulators, but their mutual interaction remains understudied. Thus, we aimed to evaluate the potential diet modulation of MED circadian oscillations.

Methods: In the first phase, a cohort study was performed comparing potential MED oscillations (morning, afternoon, and evening) among omnivorous psoriatic patients before and after a phototherapy cycle and omnivorous healthy controls. The two groups were age-, gender-, skin-type-, MED-, and diet-matched. Then, in the second phase, another cohort study was carried out comparing MED oscillations 24 h after the last phototherapeutic session only in psoriatic patients cleared with NB-UVB and undergoing different diets (vegan, vegetarian, paleo , ketogenic, intermittent circadian fasting, and omnivore). Patients with different diets were age-, gender-, and skin-type matched.

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Results: In the first phase, we enrolled only omnivores, specifically 54 PsO patients and 54 healthy individuals. Their MED before and after NB-UVB therapy changed significantly among the three different time-points (morning, afternoon, and evening) ($p < 0.001$). The time effect was statistically significant in both groups before and after phototherapy. In the second phase, we enrolled 144 PsO patients (vegan, vegetarian, paleo, ketogenic, intermittent circadian fasting, and omnivore). MED circadian oscillations preserved a significant difference also after clearance and were influenced by diet type and time of day ($p < 0.001$). In particular, vegans displayed the lowest MED values, whilst Ramadan fasting showed the highest values in morning, afternoon, and evening.
Conclusions: Diet, like other ongoing therapies, should be reported in the medical records of patients with psoriasis undergoing NB-UVB and patients with lower MEDs should be preferentially treated in the morning when the MED is higher.

Keywords: Minimal erythema dose (MED); Circadian rhythm; Psoriasis; Phototherapy; Narrow-band-UVB (NB-UVB); Diet; Intermittent circadian fasting; Vegan diet; Vegetarian diet; Paleolithic diet; Ketogenic diet

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Key Summary Points

Post-phototherapy erythema occurrence is influenced also by diet in patients with psoriasis.

Circadian oscillations of minimal erythema dose (MED) are clinically relevant only in untreated PsO patients.

Phototherapy treatment normalized circadian oscillations of MED in treated psoriasis (PsO) patients.

After clearance MED circadian oscillations are still influenced by diet type.

Diet anamnesis should be carefully recorded in PsO patients undergoing phototherapy.

INTRODUCTION

Psoriasis (PsO) is a chronic autoimmune disease that affects approximatively 40.8 million people worldwide [1], and also deeply influences patients' quality of life. A PsO patient's history may also be influenced by the great burden of comorbidities (i.e., gastrointestinal [2, 3], neurological [4, 5], respiratory [6–8], and even psychological [9, 10]). From a clinical point of view, PsO often presents a typical relapsing–remitting behavior mitigated by seasonality (in summer, PsO improves, whilst in winter it worsens) [11, 12], whilst little is known regarding the influence of circadian rhythm [13].

However, perturbation of the circadian rhythm such as night shift work [14, 15], sleep disorders [16, 17], jet-lag effect [5, 18], or even feeding time-shifts (i.e., intermittent circadian fasting) [19, 20] influence PsO severity and antipsoriatic drug response.

Furthermore, by orienting therapeutic delivery following chronomedicine principles, psoriatic patients can maximize the anti-psoriatic effects of drugs: for example, topical corticosteroids have higher efficacy if applied in the evening when keratinocytes preferentially differentiate and proliferate [21] and the pruritus peaks [22–27].

The circadian rhythm differentially regulates both the biology of skin layers [28] and the immune system [29–31]. In fact, neutrophils infiltrate more and Langerhans cells are more active during the day; conversely, macrophages and Th 17 are more functional at night when the inflammation rises up in psoriatic skin.

Immune system activation, together with vessel permeability, are the two main modulators of minimal erythema dose (MED), a measure of UVB cutaneous sensitivity, which is fundamental to orient NB-UVB therapy in PsO patients. In fact, NB-UVB remains an effective first line treatment in patients with moderate to severe psoriasis [32–34], in patients with contraindications, or in those who refuse biologics due to personal motivation, or even COVID-phobia [35, 36]. Recently, together with circadian rhythm, diet was suggested to be an important MED modulator [37–39], but their mutual interaction remains understudied. Furthermore, diet behavior is increasingly variable among PsO patients. Consequently, we encounter patients with different diet regimens (i.e., paleo, ketogenic diet, vegan, and vegetarian diets) more often in the psoriasis ambulatory clinic. We would like to know the potential influence of diet or foods on PsO, but scarce evidence is present in the literature [40].

Thus, we decided to investigate the circadian oscillation (at different times of the day) of MED in PsO patients undergoing phototherapy and characterized by different dietary habits.

MATERIALS AND METHODS

Study Design

This study was conducted in two Italian primary referral dermatological departments (IRCCS Istituto Ortopedico Galeazzi and IRCCS San Gallicano) with an experienced (> 15 years activity and > 150 patients treated per year) photobiological unit and expert photobiologists and dermatologists (> 10 years of experience in phototherapy and research). It was divided in two phases (Fig. 1):

A. The first phase was a cohort study comparing circadian oscillations of MED in morning, afternoon, and evening of the same day in patients with psoriasis, before and after clearance, and in healthy controls. The two groups were age-, gender-, skin-type-, MED-, and diet-matched. Both patients and controls were omnivores.
B. The second phase was a cohort study comparing MED circadian oscillations 24 h after NB-UVB therapy in patients whose psoriasis was already cleared, and who had different dietary habits. Patients with different diets were age-, gender-, and skin-type matched.

All subjects provided informed consent for inclusion before they participated in the study. The entire study was performed in accordance with the Declaration of Helsinki of 1975 (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/), revised in 2013, and the protocol was approved by the Ethics Committee of Saint Rafael Hospital (OSR) (Project 176/int/2020).

Inclusion and Exclusion Criteria

In this clinical study different inclusion and exclusion criteria were adopted in the two phases.

Phase 1

The inclusion criteria were: adult patients (≥ 18 years) with a diagnosis of plaque psoriasis (> 6 months), undergoing on-label treatment with NB-UVB monotherapy, compliant with medical prescriptions (< 2 therapy auto-modification/discontinuation in the previous year), and who had signed an informed consent form.

The exclusion criteria were: patients with a concurrent type of psoriasis (i.e., pustular, erythrodermic or sebopsoriasis); those with other autoimmune/inflammatory conditions [41]; those who were obese (body mass index ≥ 30 [42]); those with addictions (i.e., alcohol [Alcohol Use Disorders Identification Test > 7] [43], smokers, and marijuana/other illegal drugs

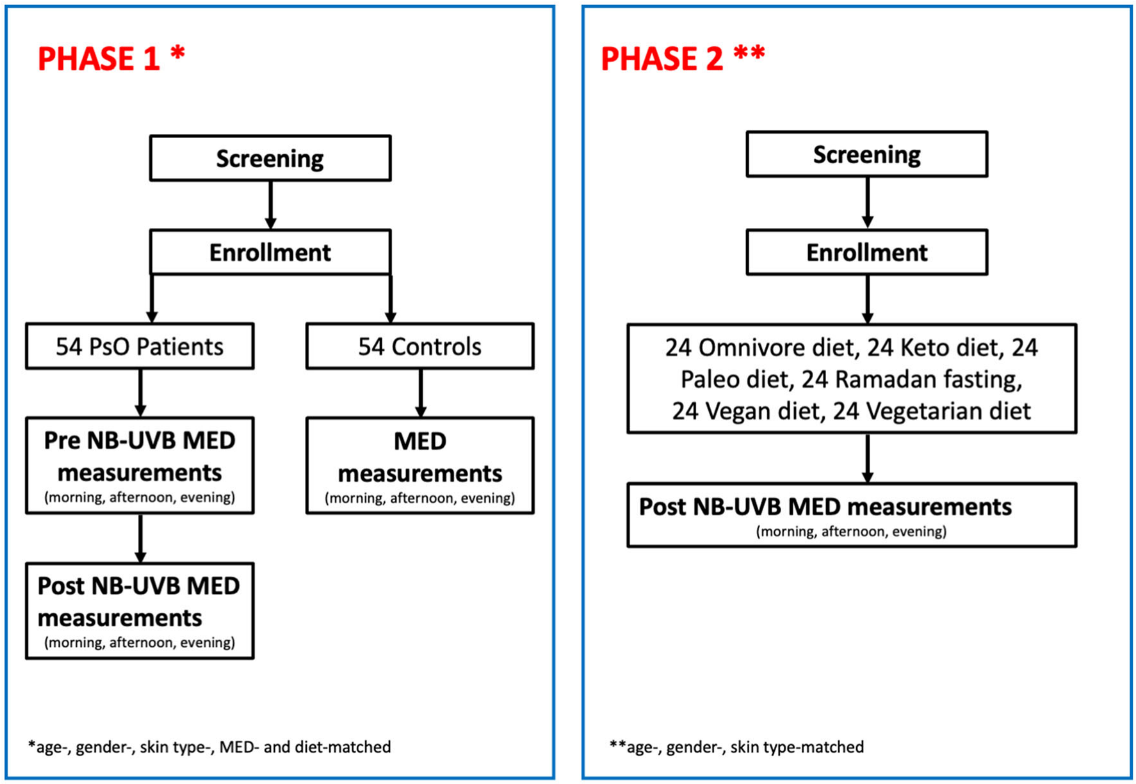


Fig. 1 Schematic representation of the 2-phase study. *MED* minimal erythema dose, *NB-UVB* narrow band-ultraviolet B, *PsO* psoriasis

users [44]); those with chronic metabolic diseases (i.e., diabetes) [45]; those who were infectious (hepatitis B and C [3, 46], HIV [47], or tuberculosis [48]) or had neoplastic diseases [49]; and any who refused to sign the informed consent form.

Parallel control individuals were otherwise healthy and were recruited from patients undergoing the annual nevi control and without concurrent dermatological/rheumatological, or gastroenterological immune disorders.

In addition, controls with concomitant dermatoses were also excluded.

Phase 2

In phase 2 of the study, all the phase 1 criteria of inclusion and exclusion were still valid, plus PsO patients also had to adhere to their habitual diet and complete a nutritional diary daily during the previous month. MED was measured in the morning, afternoon, and evening to evaluate the potential circadian oscillations post-phototherapy, a well-known modulator of the cutaneous peripheric clock.

Clinical Evaluation

Medical history and drug history were collected for every patient screened in the study, with or without psoriasis.

Patients with psoriasis were characterized using the Psoriasis Area Severity Index (PASI) [50] to quantify disease severity, and underwent the Psoriasis Epidemiology Screening Tool (PEST) [51] to exclude the occurrence of psoriatic arthritis (PsA) (a contraindication for NB-UVB in monotherapy).

Before and after each phototherapy session, patients were carefully evaluated to detect cutaneous sign of burns (i.e., erythema, vesicles) or photosensitivities/photoallergies.

Diet Evaluation

Patients and controls completed detailed dietary diaries, recording foods and beverages consumed daily, and time of consumption, during the preceding month.

Based on the dietary diary, the following diets were derived:

- Vegan diet: “the practice of dispensing with all products derived wholly or partly from animals” [52]. We also included fruitarians (eating only fruits) and crudists (eating only uncooked fruits and vegetables) in this category;
- Vegetarian diet: a diet in which patients “never ate meat, poultry and fish, or ate these foods less than once a month” [53]. In this category we included lacto-vegetarians (also eating dairy foods), ovo-vegetarians (also eating eggs), lacto-ovo vegetarians (eating both eggs and dairy foods), but we excluded pescatarians (eating fish);
- Ketogenic diet or standard ketogenic diet (SKD): a fat-rich (70% of the intake), moderate protein (20% of the intake) and low-carbohydrate (10% of the intake, < 50 g/day) diet [54]. We excluded ketogenic diets other than SKD, such as the cyclical ketogenic diet (CKD) (cycle = 5 ketogenic days + 2 high-carbohydrate days), targeted ketogenic diet (TKD) (added carbs during intensive workout), and also the high-protein ketogenic diet (HPKD) (food intake = 60% fats, 35% proteins, and 5% carbohydrates) [55];
- Paleo diet: a diet inspired by the one consumed in the Paleolithic era and characterized by a scarce dairy intake and the absence of processed foods; conversely, it is rich in fruits, nuts, vegetables, fish, eggs, and meats, as suggested in the newly proposed paleo diet score [56];
- Omnivore diet: a daily various diet that does not avoid certain food categories. A flexitarian or semi-vegetarian diet, in which patients observe “primarily a plant-based diet but includes meat, dairy, eggs, poultry and fish on occasion or in small quantities,” was included into the omnivore diet.
- Intermittent circadian fasting (Ramadan fasting): one month strict (food and beverages) fasting from dawn to sunset in line with the Islamic calendar, adjusted for location (https://www.islamicfinder.org/world/italy/). We enrolled patients following the 2021 Ramadan from April 13th to May 12th 2021.

Minimal Erythema Dose (MED) Calculation

MED was measured with a Multiport UV Solar Simulator 601 (Solar Light CO.INC: Philadelphia, PA, USA). Measures were performed in winter on covered areas (buttocks), to avoid socio-cultural and seasonal confounders, at least after 2 h after the meal in the morning (between 8 and 11 a.m.), in the afternoon (between 2 and 5 p.m.), and in the evening (between 6 and 9 p.m.) to evaluate circadian oscillations of MED. Notably, before collecting MED measurements, patients had to use a daily sensitive skin shampoo and shower gel (Ceramol Shampoo 200 ml and Ceramol Face-Body Cleansing Base 400 ml, Unifarco S.p.a., Via Cal Longa, 62, 32,035 Santa Giustina, Belluno, Italy) for 1 week, and the same emollient (Ceramol body crema, Unifarco S.p.a., Via Cal Longa, 62, 32035 Santa Giustina, Belluno, Italy) twice a day without perfumes to avoid potential photosensitizations and/or allergies [57, 58].

Sunscreens, perfumes, and emollients had to be avoided at least 4 h before MED measurement.

Narrow-Band UVB Therapy

Patients were treated with NB-UVB delivered by a PUVA Combi Light PCL 8000 phototherapy booth (Heverlee, Belgium), with 48 Phillips® TL100 W/01 tubes and a Waldmann Variocontrol dosimeter (Waldmann Medizintechnik GmbH, Villingen-Schwenningen, Germany).

In the first phototherapy session, 70% of the MED was delivered and in each subsequent session we increased the dose by 20%, halved in case of erythema, 3 times a week for 8 weeks

[59–61]. This protocol was performed to avoid photoadaptation, as previously described [62].

Statistical Analysis

Descriptive statistical analysis was carried out, computing means and standard deviations or medians for continuous variables and percentages for categorical parameters. In particular, given the longitudinal study design at different time-points, besides means, grand and marginal means (adjusted for covariates and repeated measures) were computed.

Student's *t*-test, or alternatively one-way ANOVA, was then performed to compare means between psoriatic subjects against healthy subjects and between different diet groups. The χ^2 test, or alternatively Fisher's exact test (for an expected frequency lower than five), was used to address differences in the distribution of the categorical variables between the same groups. A mixed ANOVA was performed to quantify the group effect, both by psoriasis presence and by diet, together with the circadian oscillation effect on MED. Similarly, a MANOVA was conducted to adjust for other characteristics of the sample, such as age, gender, and skin type. For all the continuous dependent variables, non-significant departures from the normal distribution and homogeneity of variances were checked (with the Shapiro–Wilk and Levene tests, respectively) prior to proceeding with parametric analysis.

RStudio software was used for the analysis.

RESULTS

Circadian MED Oscillations in Psoriatic Patients Before and After NB-UVB Therapy (Phase 1)

Patient Characteristics

We recruited 108 subjects: 54 PsO patients and 54 healthy individuals. PsO patients displayed a PASI of 4.69 ± 1.37 (median 5) and 27 (50%) also had PsO family history. The most common Fitzpatrick skin-type (phototype) was III (n = 42, 38.9%), followed by II (n = 24, 22.2%), IV (n = 20, 18.5%), I (n = 12, 11.1%), and V/VI were the least common (n = 10, 9.3%) (Table 1). In line with matching criteria, no differences were present for age-, gender-, skin-type-, MED- or diet.

MED Values Before Clearance

Comparing MED oscillations in morning, afternoon and evening between psoriasis patients and healthy controls no statistical difference was found (Fig. 2A), conversely comparing circadian oscillations of MED in the whole day only psoriasis patients had stitistically significant oscillations (Table 2).

Despite intergroup differences in MED not being significant, intragroup differences in psoriatic untreated patients resulted highly significant differences ($p < 0.001$) (Fig. 2B).

There was a statistically significant ($p < 0.001$) difference in MED values before and after NB-UVB only in psoriatic patients.

Diet-Related Modifications of MED Circadian Oscillation in Remitted Psoriatic Patients Treated with Phototherapy (Phase 2)

Patient Characteristics

One hundred forty-four PsO patients were recruited (mean age 40.29 ± 7.39 years, 66 females, 45.8%, 78 males, 54.2%). The majority of the subjects [95 (66.0%)] had skin-type III, while only 49 (34.0%) had skin-type IV. Patients were also categorized according to their type of diet: vegans, vegetarians, following paleo or ketogenic diets, or observing Ramadan fasting (n = 24 for each group). In line with matching criteria, no statistically significant differences were detected for age-, gender-, or skin-type in the six considered groups (Table 3).

Diet and Time of the Day are the Main Determinants of MED Circadian Oscillations

After NB-UVB treatment and complete clinical resolution, psoriatic patients still maintain circadian oscillations of MED that are influenced by time effect and diet ($p < 0.001$), as reported by both two-way mixed ANOVA and mixed MANOVA (Table 4).

Table 1 Group differences in main characteristics of recruited patients for phase 1

Parameter	Psoriatic (*N* = 54)	Healthy (*N* = 54)	*p*
Age, mean ± SD; median, years	39.94 ± 10.22; 41	39.98 ± 10.27; 43	0.985
Gender, *N* (%)			1.00
Males	27 (50.0)	27 (50.0)	
Females	27 (50.0)	27 (50.0)	
PASI, mean ± SD; median	4.69 ± 1.37; 5	–	–
Fitzpatrick skin type, *N* (%)			0.881
I	6 (11.1)	6 (11.1)	
II	12 (22.2)	12 (22.2)	
III	23 (42.6)	19 (35.2)	
IV	8 (14.8)	12 (22.2)	
V and VI	5 (9.3)	5 (9.3)	

PASI Psoriasis Area Severity Index, *SD* standard deviation

Remarkably, MED results in the Ramadan fasting group were statistically different in the morning, afternoon, and evening from MED results of patients practicing other diets. Ramadan patients displayed both globally, and at the considered timepoints, the highest MED, while vegans displayed the lowest MED (Table 4).

In the morning, MED values for the ketogenic diet were statistically different from omnivores, Ramadan and vegans, while the paleo diet differed in terms of MED from Ramadan and vegan. Then, vegans differed from all other diets except omnivores. Vegetarians differed only from vegans and Ramadan fasting.

In the afternoon, MED values of Ramadan fasting patients and vegans were statistically significantly different to all the other considered groups. Omnivores differed from paleo diet patients. Ketogenic, paleo and omnivore diets did not differ.

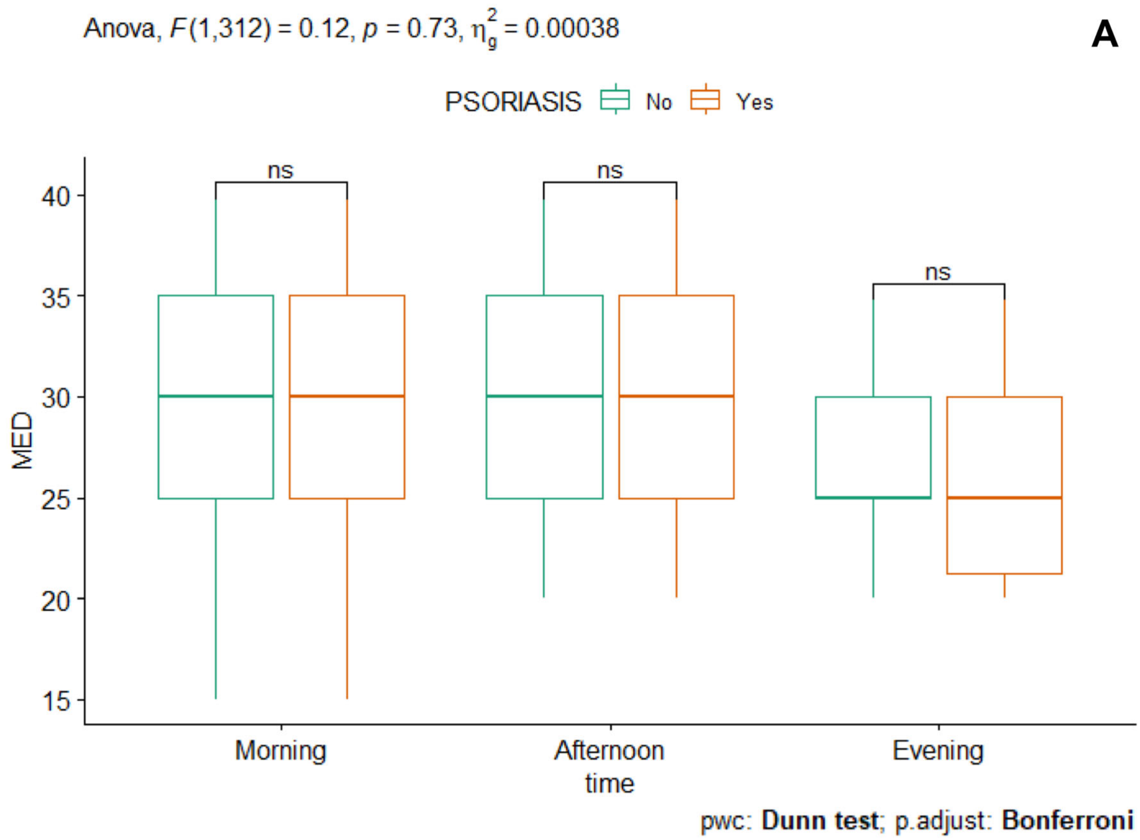
Likewise, in the evening, Ramadan fasting patients and vegans exhibited MED values statistically significantly different to all the other considered groups (Fig. 3A).

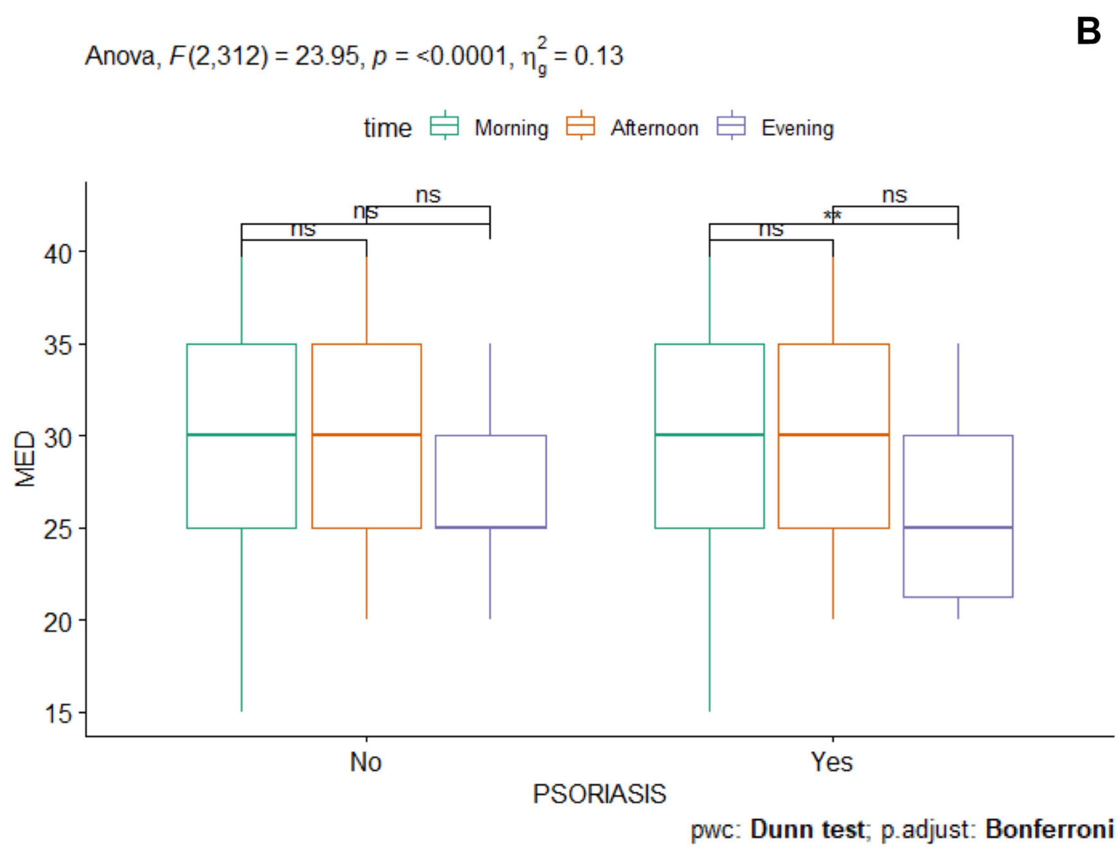
Interestingly, when we evaluated the different diets separately, we did not find a statistically significant difference in MED measured in the morning, afternoon, or evening, except for vegan and vegetarian diets. Furthermore, vegan patients still showed differences in MED measured in the morning and in the afternoon (Fig. 3B).

DISCUSSION

In the present study, we found that circadian oscillations of MED exist in both healthy and PsO patients: MED decreases from the morning to the evening. In the past decade, several clinical determinants of MED have been found to have conflicting results, from skin color (assessed with colorimetric methods) [63, 64] to skin phototype [65–67], gender [65, 66], age [66], and meteorological factors [64, 67–69].

All these potential modulators act on three main biological mechanisms: melanin production, skin thickness, and vessels. Melanin and hemoglobin are the main chromophores of human skin; in particular, melanin increases UVB reflection, thus increasing MED. Conversely, vessel vasodilatation decreases refraction (thinner skin) and increases hemoglobin-dependent UVB absorption, thereby decreasing MED. Thus, MED is mainly determined by the


Anova, F(1,312) = 0.12, p = 0.73, η²g = 0.00038
A
PSORIASIS No Yes
ns
ns
ns
MED
40
35
30
25
20
15
Morning
Afternoon
Evening
time
pwc: Dunn test; p.adjust: Bonferroni


Anova, F(2,312) = 23.95, p = <0.0001, η²g = 0.13
B
time Morning Afternoon Evening
ns
ns
ns
ns
**
ns
MED
40
35
30
25
20
15
No
Yes
PSORIASIS
pwc: Dunn test; p.adjust: Bonferroni

◀**Fig. 2** **A** Intergroup differences of MED in the morning, afternoon, and evening. **B** Intragroup differences between MED in the morning, afternoon, and evening. *MED* minimal erythema dose

interaction of melanin and hemoglobin, and external exposure (exposome) [70] (i.e., drugs or temperature) [64, 71] or internal factors (i.e., fever) can alter MED [72].

Physiological internal factors are mainly controlled by the circadian rhythm, a well-known peripheral clock in the skin controlling and regulating keratinocyte proliferation and differentiation, melanocyte metabolism, trans-epidermal water loss (TEWL), gland function, and even vessel tone [13]. Likewise, we demonstrated, for the first time, MED circadian oscillations in both patients with psoriasis and healthy controls, finding that MED is higher in the morning and tends to decrease in the evening. This aspect has a practical implication because patients with low MED (20–25 mJ/cm^2) should be preferentially treated in the morning to minimize the possibility of burns and increase the session implementation, especially if the patient is vegan.

Remarkably, psoriasis represents a pathological internal condition characterized by both cutaneous and systemic inflammation capable of creating circadian dysfunction both in peripheral and in central clocks [28, 73]. The central clock dysfunction in psoriatic patients manifests with sleep disorders such as obstructive sleep apnea and insomnia, two factors negatively influencing quality of life [74–76]. Furthermore, keratinocyte hyperplasia, neutrophil chemoattraction in the skin, Th1/Th17 dysregulation, and neoangiogenesis represent the clinical hallmarks of psoriasis but are also related to circadian rhythm de-regulation in the cutaneous peripheral clock [38] and to MED [64].

Focusing on the external factors capable of modulating MED, our team has previously shown that diet modulates cutaneous severity in both PsO [19] and PsA [20] patients, and that vegan/vegetarian diets modify cutaneous photosensitivity to UVB [77]. In the present study, we found that diets can impact MED values at different daily time-points, with MED values significantly lower in vegan patients,

Table 2 ANOVA and MANOVA psoriasis group and circadian oscillation effects significance

	Time	Group		
		Psoriatic (N = 54)	**Healthy (N = 54)**	***p* Group effect**
MED mean ± SD; median*				
	Morning (8–11 am)	29.91 ± 6.10; 30	29.44 ± 6.41; 30	
	Afternoon (2–5 pm)	28.89 ± 5.80; 30	29.07 ± 5.91; 30	
	Evening (6–9 pm)	26.39 ± 4.99; 25	26.94 ± 4.99; 25	
Two-way Mixed ANOVA				0.884
p Time effect	< 0.001			
p Group and Time effect	0.804			
Mixed MANOVA				0.729
p Time effect	< 0.001			
p Group and Time effect	0.527			

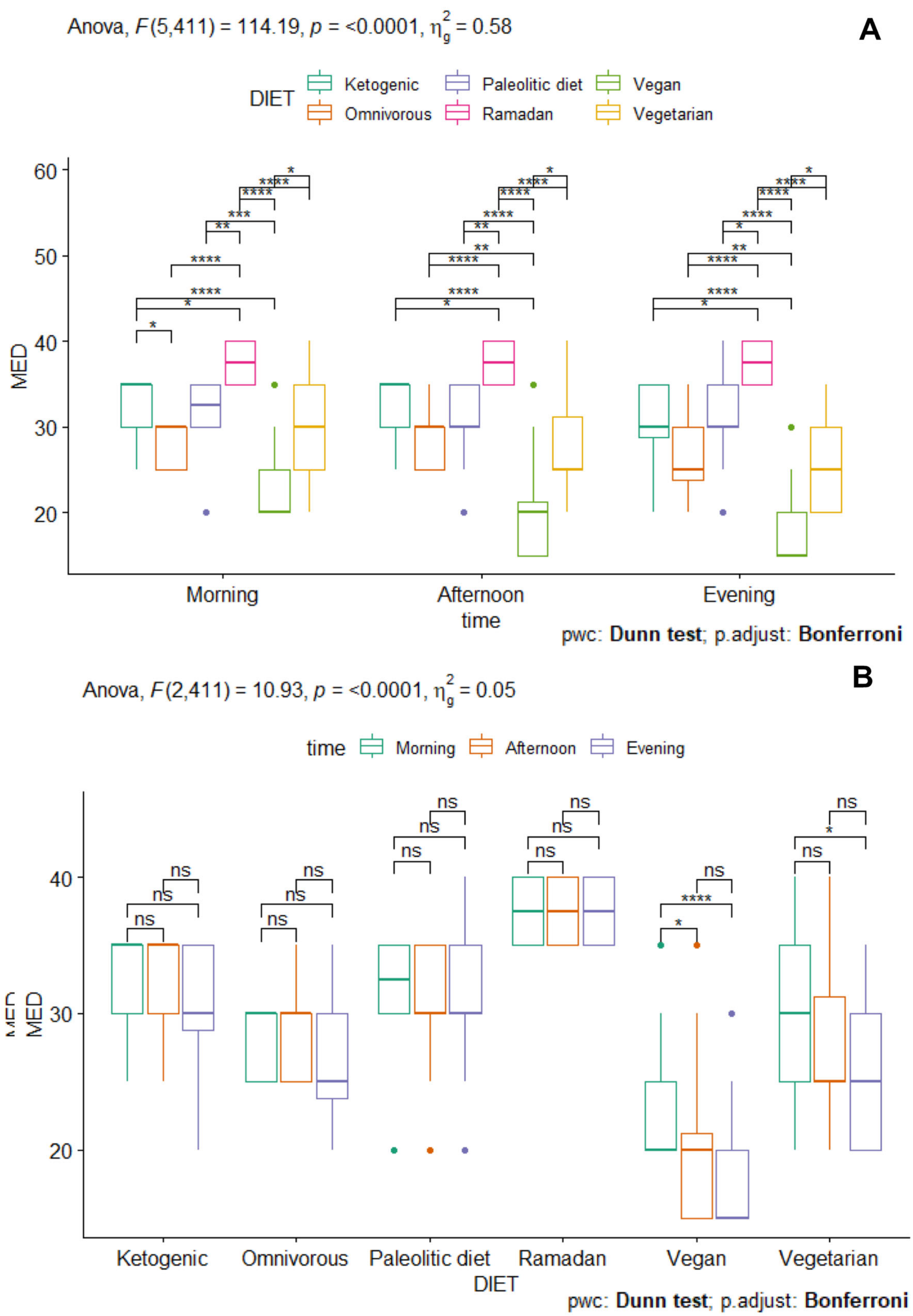
*For psoriatic subjects the baseline MED values were considered (before clearance)

Table 3 Diet group characteristics among patients recruited for the second phase study

Parameter	Ketogenic diet (N = 24)	Omnivorous diet (N = 24)	Paleo (N = 24)	Ramadan fasting (N = 24)	Vegan (N = 24)	Vegetarian diet (N = 24)	p
Age, mean ± SD; median, years	40.08 ± 7.07; 41	40.54 ± 7.21; 41	40.29 ± 7.51; 40	40.33 ± 7.76; 40	40.08 ± 7.80; 40.5	40.38 ± 7.77; 40	1.00
Gender, N (%)							1.00
Males	13 (54.2)	13 (54.2)	13 (54.2)	13 (54.2)	13 (54.2)	13 (54.2)	
Females	11 (45.8)	11 (45.8)	11 (45.8)	11 (45.8)	11 (45.8)	11 (45.8)	
Fitzpatrick skin type, N (%)							1.00
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
III	15 (62.5)	16 (62.7)	16 (62.7)	16 (62.7)	16 (62.7)	16 (62.7)	
IV	9 (37.5)	8 (37.3)	8 (37.3)	8 (37.3)	8 (37.3)	8 (37.3)	
V and VI	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Table 4 ANOVA and MANOVA diet group and circadian oscillation effects significance

	Time	Group						
		Ketogenic diet (N = 24)	**Omnivorous diet (N = 24)**	**Paleo diet (N = 24)**	**Ramadan fasting (N = 24)**	**Vegan diet (N = 24)**	**Vegetarian diet (N = 24)**	***p* Group effect**
MED mean ± SD; median*								
	Morning (8–11 am)	32.29 ± 4.16; 35	27.71 ± 2.54; 30	31.67 ± 4.34; 32.5	37.50 ± 2.55; 37.5	23.54 ± 5.00; 20	29.38 ± 5.58; 40	
	Afternoon (2–5 pm)	32.08 ± 4.15; 35	28.54 ± 3.75; 30	30.62 ± 4.73; 30	37.50 ± 2.55; 37.5	20.21 ± 5.21; 20	28.12 ± 6.05; 25	
	Evening (6–9 pm)	30.62 ± 4.96; 30	26.25 ± 5.16; 25	30.42 ± 5.69; 30	37.50 ± 2.55; 37.5	17.71 ± 3.90; 15	25.00 ± 5.32; 25	
Two-way Mixed ANOVA								< 0.001
p Time effect	< 0.001							
p Group and Time effect	0.080							
Mixed MANOVA								< 0.001
p Time effect	< 0.001							
p Group and Time effect	0.079							


A
Anova, F(5,411) = 114.19, p = <0.0001, η²g = 0.58
DIET
Ketogenic
Omnivorous
Paleolitic diet
Ramadan
Vegan
Vegetarian
MED
Morning
Afternoon
Evening
time
pwc: Dunn test; p.adjust: Bonferroni
B
Anova, F(2,411) = 10.93, p = <0.0001, η²g = 0.05
time
Morning
Afternoon
Evening
MED
Ketogenic
Omnivorous
Paleolitic diet
Ramadan
Vegan
Vegetarian
DIET
pwc: Dunn test; p.adjust: Bonferroni

◂**Fig. 3** **A** Intergroup differences between MED in the morning, afternoon, and evening. **B** Intragroup differences between MED in the morning, afternoon, and evening. *MED* minimal erythema dose

confirming and expanding our previous study [77], and MED values higher in those following Ramadan fasting. In fact, different dietary compounds modify microRNA expression [78], gut microbiome [79], and clinical severity of psoriasis [78]: three well-known modulators of MED. Similarly, the content, quality, and dietary sources of macronutrients, including fats, carbohydrates, and proteins, may modulate cell/tissue inflammation, oxidative stress, proliferation/differentiation, and clinical severity of psoriasis [80]. Interestingly, the afternoon MED differences in patients following omnivore, ketogenic or paleo diets disappeared. The ketogenic diet [81], characterized by a low carbohydrate intake along with a high intake of protein and fat, has been demonstrated to improve clinical symptoms and biochemical and inflammatory markers in PsO patients. Similarly, Ramadan fasting, with the corresponding changes in sleep–wake cycles, has been shown to be beneficial in terms of PsO severity [19]. Data on paleo diet in psoriasis are very scarce, but recently a US survey in PsO patients has found self-reported symptom improvement with the paleo diet [39]. Further research is, however, warranted to confirm and mechanistically investigate the effects of diets and their components on psoriasis management.

Furthermore, some dietary compounds, including polyphenols, vitamins, fatty acids, or the macronutrient content of the diet, have been shown to affect the expression and/or function of the circadian clock machinery in different peripheral tissues, with the ability to also function as circadian clock drivers (zeitgebers) of biological processes, either impairing or restoring circadian rhythmicity [82, 83]. Further investigation is needed to assess the specific effects of dietary compounds on the skin circadian clock system in relation to psoriasis-linked circadian dysfunction.

Interestingly, after NB-UVB treatment, MED circadian oscillations are modified and increase from morning to evening only in vegan psoriatic patients. In fact, NB-UVB treatment modifies the cutaneous reactivity to external exposures via (a) the migration of Langerhans cells to lymph nodes [84] and (b) regularizing the skin microbiome dysregulation due to psoriatic inflammation [36, 85], and these effects are magnified by quantities of furocumarins ingested, as seen in the vegan diet. Circadian reset of MED after treatment also suggests that cutaneous psoriasis should always be treated with the principal of chronomedicine to avoid immunological dysfunction.

Skin exposure to NB-UVB also modulates the human gut microbiome and increases vitamin D serum levels linearly with *Lachnospiraceae* prevalence [86]. Thus, a proper diet may act synergically with anti-psoriatic drugs to re-establish cutaneous homeostasis and to extinguish peripheral clock dysregulation.

In this study, we focused on circadian oscillations and diet in psoriatic non-obese patients that had no addictions (i.e., smoking or alcohol), so future studies should further investigate these patient subsets that display contraindication to first line systemic treatments (i.e., methotrexate). NB-UVB was also evaluated as a single therapy, while in real life, phototherapy is commonly used as a combination therapy to achieve PASI 100 or even to counteract a gradual loss of response to a biologic drug. Further studies should also evaluate the knowledge of, attitude to, and practice of sun-exposure in patients undergoing NB-UVB.

Thus, detailed knowledge of MED determinants is of paramount importance in order to increase NB-UVB efficacy while decreasing the frequency of burns.

CONCLUSIONS

The present study further strengthens the concept of both chronomedicine and precision medicine, showing that NB-UVB should be preferentially delivered in the morning, and phototherapy protocols should account for a patient's diet. In contrast with Rodriguez et al.

[87], MED should always be calculated before starting NB-UVB because (a) internal and external factors may alter MED, (b) MED is not directly derived from the skin type, and (c) circadian rhythm can modify cutaneous UVB susceptibility.

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Compliance with Ethics Guidelines. Saint Rafael Hospital (OSR) local ethical committee approved in 28.05.2021 the study protocol 176/int/2020 and the current study represents a post-hoc analysis. The study fulfilled all the prin-ciples of Helsinki Declaration. Informed consent was obtained from all subjects involved in the study.

Data Availability. The data presented in this study are available on request from the corresponding author (dr.giovanni.damiani@gmail.com). The data are not publicly available due to privacy issues.

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